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Natural Herbs as Anticancer Drugs

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Abstract: This article has been made to review some medicinal plants used for the treating cancer disease . The plant sources of India are likely to provide effective anticancer agents. Herbs have a vital role in the prevention and treatment of cancer. Examples are provided in this review of promising bioactive compounds obtained from various plants with medicinal and other therapeutic uses. The photochemical exploration of these herbs has contributed to some extent in this race for the discovery of new anticancer drugs. In recent years owing to the fear of side effects people prefer to use of natural plant products for cancer treatment. This review also helps to summarize the diverse methodologies and various ways to evaluate the potential natural compounds having anticancer activity. Although drug discovery from medicinal plants continues to provide an important source of new drug leads, numerous challenges are encountered including the procurement of plant materials and their selection.
Keywords: Medicinal plants, Anticancer agents, Bioactive compounds.

Introduction

Cancer is a leading cause of mortality, and it strikes more than one-third of the world's population and it's the cause of more than 20% of all deaths. Among the causes for cancer are tobacco , viral infection, chemicals, radiation, environmental factors, and dietary factors.[1] Surgery, chemotherapy and radiotherapy are the main conventional cancer treatment often supplemented by other complementary and alternative therapies in China.[2] Plants has been used as an age old remedy of cancer history of use in the treatment of cancer. Extensive research at Sandoz laboratories in Switzerland in the 1960s and 1970s led to the development of etoposide and teniposide as clinically effective agents which are used in the treatment of lymphomas, bronchial and testicular cancer.[3] These plants may promote host resistance against infection by re-stabilizing body equilibrium and conditioning the body tissues. Several reports describe that the anticancer activity of medicinal plants is due to the presence of antioxidants present in them. In fact, the medicinal plants are easily available, cheaper and possess no toxicity as compared to the modern (allopathic) drugs.[4] The development of novel plant-derived natural products and their analogs for anticancer activity details efforts to synthesize new derivatives based on bioactivity- and mechanism of action-directed isolation and characterization coupled with rational drug design - based modification.[5]

Oncogenes are regulators of cellular communication with the outside environment. They are derived through the mutation of proto-oncogenes. Mutated oncogenes are stimulated by exposure to chemical, environment or viral carcinogens, which leads to cell changes and they produce proteins which are either wrongly expressed within their normal cell or expressed in inappropriate tissue which leads to cellular proliferation and there by result in cancer formation . Tumor suppressor genes are intended to keep oncogenes in check by halting uncontrolled

cellular growth. In direct opposition to oncogenes, which induce cancer when stimulated or amplified, tumor suppressor genes promote cancer when inactivated or attenuated. Two of the most prevalent tumor suppressor genes involved in the generation of cancer are p53 and retinoblastoma or Rb.[6]

Anticancer Plants

Acronychia Bauer:-Utilizing a differential extraction technique for the examination of the bark of the Australian plant *Acronychia Baueri* Schott (*Bauerella australiana* Borzi), has resulted in the isolation of the triterpene lupeol and the alkaloids melicopine, acronycine, and normelicopidine. The experimental anti tumor activity associated with the crude alkaloidal mixture obtained from the ether extract has been shown to be attributable to acronycine. Experimental evidence is herein given, showing acronycine to have the broadest antitumor spectrum of any alkaloid isolated to date in these laboratories. By virtue of its being chemically unrelated to any of the presently utilized antitumor agents it represents a new lead in the search for agents effective in the chemotherapeutic management of human neoplasms.[7]

Garlic (*Allium sativum* L.) has a long history of being as a food having a unique taste and odor along with some medicinal qualities. Modern scientific research has revealed that the wide variety of dietary and medicinal functions of garlic can be attributed to the sulfur compounds present in or generated from garlic. Although garlic produces more than 20 kinds of sulfide compounds from a few sulfur-containing amino acids, their functions are different from one another; e.g., allicin, methyl allyl trisulfide, and diallyl trisulfide have antibacterial, antithrombotic, and anticancer activities, respectively.[8]

Garlic [*Allium sativum*] is among the oldest of all cultivated plants. It has been used as a medicinal agent for thousands of years. It is a remarkable plant, which has multiple beneficial effects such as antimicrobial, antithrombotic, hypolipidemic, antiarthritic, hypoglycemic and antitumor activity. A number of studies have demonstrated the chemopreventive activity of garlic by using different garlic preparations including fresh garlic extract, aged garlic, garlic oil and a number of organosulfur compounds derived from garlic. The chemopreventive activity has been attributed to the presence of organosulfur compounds in garlic. However it not understood, but several mode of action this is achieved is not fully understood, but several modes of action have been proposed. These include its effect on drug metabolizing enzymes, antioxidant properties and tumor growth inhibition. Most of these studies were carried out in the animal models. Also, recent research has been focused on the antimutagenic activity of garlic. Recently, it has been observed that aged garlic extract, but not the fresh garlic extract, exhibited free radical scavenging activity. The two major compounds in aged garlic, S-allylcysteine and S-allylmercapto-L-cysteine, which has had the highest radical scavenging activity. In addition, some organosulfur compounds derived from garlic, include S-allylcysteine, have been found to retard the growth of chemically induced and transplantable tumors in several animal models. Therefore, the consumption of garlic may provide some kind of protection from cancer development.[9]

Table No.1:Types of cancer and common oncogenic or tumor suppressor gene origin .

Cancer type	Common oncogenic or tumor suppressor gene origin
Chronic myelogenous leukemia	Bcr-abl proto-oncogene translocation
Follicular lymphoma	Bcl-2 amplification, myc mutation
Sporadic thyroid cancer	Ret mutation
Colorectal and gastric cancer	APC gene mutation
Familial breast and ovarian cancer	BRCA1, BRCA2 mutation
Invasive ductal breast cancer	HER-2 amplification
Familial melanoma	$P16^{INK4A}$ mutation
Childhood neuroblastoma and small cell lung cancer	N-myc amplification
Leukemia, breast, colon, gastric and lung cancer	c-MYC amplification
Renal cell cancer	Von Hippel-Lindaugene (VHL) dysfunction

Artemisia capillaries is a major important food and medicinal resource found in Korea. In order to confirm the biological activities of *Artemisia capillaries*, antioxidant and anticancer activities from in vitro assays were investigated. The *Artemisia capillaries* methanol (MeOH) extracts were used for the evaluation of DPPH(2,2-diphenyl-1-picrylhydrazyl) scavenging, total phenolic content, total flavonoid content, hydroxyl radical (・OH) scavenging, reducing power assay as antioxidant activity, as well as anticancer activities as MTT assay. As a result, the *Artemisia capillaries* MeOH extracts showed potent antioxidative activity and anticancer activity in vitro. These results suggest that the *Artemisia capillaries* MeOH extracts have a potential alleviated oxidation process, cell motility activity, and tumorigenesis. [10]

Astragalus membranaceus, a commonly used Chinese medicinal plant, has been shown to be capable of restoring the impaired T cell functions in cancer patients. The *in vitro* and *in vivo* anti-tumor effects of *A. membranaceus* were investigated. Five bioactive fractions were isolated from the root of *A. membranaceus*, the fraction designated as AI was found to be the most potent among the five fractions with respect to its mitogenicity on murine splenocytes. Besides investigating the cytostatic effect of AI, its activities on macrophage function, tumor necrosis factor production, induction of lymphokine-activated killer cell and tumor cell differentiation were also examined. The macrophage-like tumors and the myeloid tumors were found to be more sensitive to the cytostatic activity of AI, whereas the fibroblast-like tumors and the mouse Ehrlich ascites tumor appeared to be relatively resistant. Moreover, AI could effectively suppress the *in vivo* growth of syngeneic tumor in mice. Results showed that murine macrophage pretreated with AI had increased *in vitro* and *in vivo* cytostatic activities towards MBL-2 tumor. AI could also act as a priming agent for tumor necrosis factor production in tumor-bearing mice. Preincubation of mouse splenocytes with AI could induce *in vitro* lymphokine-activated killer-like activity towards WEHI-164 cell. Furthermore, AI was able to induce monocytic differentiation of both human and murine cells *in vitro*. AI administered *in vivo* could even partially restore the depressed mitogenic response in tumor-bearing mice. Collectively, the results showed that *A. membranaceus* could exhibit both *in vitro* and *in vivo* anti-tumor effects, which might be achieved through activating the anti-tumor immune mechanism of the host.[11]

The in vitro inhibitory effect of *Beta vulgaris* (beet) root extract on Epstein-Barr virus early antigen (EBV-EA) induction using Raji cells revealed a high order of activity compared to capsanthin, cranberry, red onion skin and short and long red bell peppers. An in vivo anti-tumor promoting activity evaluation against the mice skin and lung bioassays also revealed a significant tumor inhibitory effect. The combined findings suggest that beetroot ingestion can be one of the useful means to prevent cancer. [12]

Green tea is an aqueous infusion of dried unfermented leaves of *Camellia sinensis* (Family *Theaceae*) from which numerous biological activities have been reported including antimutagenic, antibacterial, hypocholesterolemic, antioxidant, antitumor and cancer preventive activities. From the aqueous-alcoholic extract of green tea leaves, six compounds (+)-gallocatechin (GC), (-)-epicatechin (EC), (-)-epigallocatechin (EGC), (-)-epicatechin gallate (ECG), (-)-epigallocatechin gallate (EGCG) and caffeine, were isolated and purified. Together with (+)-catechin, these compounds were tested against each of four human tumor cells lines (MCF-7 breast carcinoma, HT-29 colon carcinoma, A-427 lung carcinoma and UACC-375 melanoma). The three most potent green tea components against all four tumor cell lines were EGCG, GC and EGC. EGCG was the most potent of the seven green tea components against three out of the four cell lines (i.e. MCF-7 breast cancer, HT-29 colon cancer and UACC-375 melanoma). On the basis of these extensive in vitro studies, it would be of considerable interest to evaluate all three of these components in comparative preclinical in vivo animal tumor model systems before final decisions are made concerning which of these potential chemopreventive drugs should be taken into broad clinical trials. [13]

Camptothecin (CPT) is an anticancer and antiviral alkaloid produced by the Chinese tree *Camptotheca acuminata (Nyssaceae)* and some other species belonging to the families *Apocynaceae, Olacaceae, and Rubiaceae*. Bark and seeds are currently used as sources for the drug. Several attempts have been made to produce CPT from cell suspensions; however, the low yields obtained limit this approach. Cultures of differentiated cell types may be an alternative source of alkaloid production. Hairy root cultures of *C. acuminata* were established from tissue transformed with *Agrobacterium rhizogenes* strains ATCC 15834 and R-1000. Integration of these genes are responsible for the hairy-root phenotype (*rol* genes) into the plant genome was verified by DNA gel blot analysis. The hairy roots produce and secrete CPT as well as the more potent and less toxic natural derivative, 10-hydroxycamptothecin (HCPT), into the medium. Remarkably, the cultures were able to synthesize the

alkaloids at levels equal to, and sometimes greater than, the roots in planta, i.e., 1.0 and 0.15 mg/g dry weight for CPT and the HCPT, respectively.[14]

Catharanthus roseus produces low levels of two dimeric terpenoid indole alkaloids, vinblastine and vincristine, which are widely used in cancer chemotherapy. The dimerization reaction leading to *α*-3', 4'-anhydrovinblastine is a key regulatory step for the production of the anticancer alkaloids in planta has an potential application in the industrial production of two semisynthetic derivatives also used as anticancer drugs. The cloning, characterization, and subcellular localization of an enzyme with anhydrovinblastine synthase activity identified as the major class III peroxidase present in *C. roseus* leaves and was named an *CrPrx1*. The deduced amino acid sequence corresponds to a polypeptide of 363 amino acids including an N-terminal signal peptide showing the secretory nature of CrPrx1. *CrPrx1* has a two-intron structure and is present as a single gene copy. Phylogenetic analysis indicates that *CrPrx1* belongs to an evolutionary branch of vacuolar class III peroxidases whose members seem to have been recruited for different functions during evolution. Expression of a green fluorescent protein-*CrPrx1* fusion confirmed the vacuolar localization of this peroxidase, the exact subcellular localization of the alkaloid monomeric precursors and dimeric products. Expression data further supports the role of *CrPrx1* in *α*-3', 4'-anhydrovinblastine biosynthesis, indicating the potential of *CrPrx1* as a target to increase alkaloid levels in the plant.[15]

Inonotus obliquus :-The Chaga mushroom (*Inonotus obliquus*) has been used in folk medicine to treat cancers. However, limited information exists on the underlying anticancer effects of the major component of *I. obliquus in vivo* studies . It is hypothesized that the pure compounds (3β-hydroxy-lanosta-8, 24-dien-21-al, inotodiol and lanosterol, respectively) isolated from *I. obliquus* would inhibit tumor growth in Balbc mice bearing Sarcoma-180 cells (S-180) *in vivo* and growth of human carcinoma cells *in vitro*. To test this hypothesis, the growth inhibition of each subfraction isolated from *I. obliquus* on human carcinoma cell lines (lung carcinoma A-549 cells, stomach adenocarcinoma AGS cells, breast adenocarcinoma MCF-7 cells, and cervical adenocarcinoma HeLa cells) was tested *in vitro*. Then, after S-180 implantation, the mice were fed a normal chow supplemented with 0, 0.1 or 0.2 mg of subfraction 1, 2 or 3 per mouse per day. All of the subfractions isolated from *I. obliquus* showed significant cytotoxic activity against the selected cancer cell lines *in vitro*. Subfraction 1 was more active than subfraction 2 and subfraction 3 against the A549, AGS and MCF-7 cancer cell lines *in vitro*. In *in vivo* results, subfraction 1 isolated from *I. obliquus* at concentrations of 0.1 and 0.2 mg/mouse per day significantly decreased tumor volume by 23.96% and 33.71%, respectively, as compared with the control. Subfractions 2 and 3 also significantly inhibited tumor growth in mice bearing S-180 as compared with the control mouse tumor. Subfraction 1 isolated from *I. obliquus* showed greater inhibition of tumor growth than subfractions 2 and 3, which agrees well with the *in vitro* results. The results suggest that *I. obliquus* and its compounds in these subfractions isolated from *I. obliquus* could be used as natural anticancer ingredients in the food and/or pharmaceutical industry.[16]

Anticancer activity of the rhizomes of turmeric *(Curcuma longa)* was evaluated by italies in vitro using tissue culture methods and in vivo in mice using Dalton's lymphoma cells grown as ascites form. Turmeric extract inhibited the cell growth in Chinese Hamster Ovary (CHO) cells at a concentration of 0.4 mg/ml and was cytotoxic to lymphocytes and Dalton's lymphoma cells at the same concentration. Cytotoxic effect was found within 30 min at room temperature (30 C). The active constituent was found to be 'curcumin' which showed cytotoxicity to lymphocytes and Dalton's lymphoma cells at a concentration of 4 mg/ml. Initial experiments indicated that turmeric extract and curcumin reduced the development of animal tumours.[17]

Curcuma zedoaria belonging to the family *Zingiberaceae* has been used in the traditional system of medicine in India and Southwest Asia in treating many human ailments and is found to possess many biological activities. The rationale of the present study was to isolate, identify, and characterize antitumour principles from the rhizomes of *Curcuma zedoaria*, to assess its cytotoxic effects on human and murine cancer cells, to determine its apoptosis inducing capacity in cancer cells, and to evaluate its tumour reducing properties in *in vivo* mice models. Isocurcumenol was characterized as the active compound by spectroscopy and was found to inhibit the proliferation of cancer cells without inducing significant toxicity to the normal cells. Fluorescent staining exhibited the morphological features of apoptosis in the compound-treated cancer cells. *In vivo* tumour reduction studies revealed that a dose of 35.7mg/kg body weight significantly reduced the ascitic tumour in DLA-challenged mice and increased the lifespan with respect to untreated control mice.[18]

Three constituents, β-sitosterol, laserine and epilaserine, were isolated from the lipophilic fraction of *Daucus carota*. Among the 3 constituents,

epilaserine showed significantly inhibitory effect on leukemia cell, HL-60.[19]

Licochalcone (LA) is a novel estrogenic flavonoid isolated from PC-SPES composition herb licorice root *(Glycyrrhiza Glabra)* which show significant antitumor activity in various malignant human cell lines. To better understand its anti-Cancer activities investigation were carried out in LA-elicited growth control and induction of apoptosis using androgen-independent p53-null PC-3 prostate cancer cells. LA induced modest level of apoptosis but had more pronounced effect on cell cycle progression arresting cells in G2/M, accompanied by suppression of cyclin B1 and cdc2. It also inhibited phosphorylation of Rb, specifically phosphorylation of S780 with no change of phosphorylation status of T821, decreased expression of transcription factor E2F concurrent with reduction of cyclin D1, down-regulation of CDKs 4 and 6, but increased cyclin E expression. These findings provide mechanistic explanation for LA activity and suggest that it may be considered as a chemopreventive agent and its anticancer properties should be further explored.[20]

Ethanolic extract of *Hydrastis canadensis* has been tested for its possible anti-cancer potentials against p-dimethylaminoazobenzene (p-DAB) induced hepatocarcinogenesis in mice. A critical analysis of results of this investigation shows anti-cancer potentials of the drug suitable for use as a supportive complementary medicine in liver cancer.[21]

The aqueous extract of *Larrea divaricata* has an antiproliferative activity on T lymphoma (BW 5147) cells in culture. Moreover the extract has *in vivo* antitumor activity when it was administered to a pregnant rat which had a spontaneous mammary tumor. The effect of an extract of *Larrea divaricata* was studied on a mammary carcinoma chemically induced with N-nitrosomethylurea in females rats. The extract was administered at a dose of 250 mg/kg three times each week by two different routes, subcutaneous (s.c.) and intratumoral (i.t.). the investigation shows that the aqueous extract of this plant has an *in vivo* antitumor activity with the intratumor route being most effective in induction of tumor regression.[22]

The cytotoxicity effect of tomato *(Lycopersicum esculentum)* leaves (methanol extract) on cancer cells to address potential therapeutic in MCF-7 breast cancer cell lines and its toxicity towards Vero cells was shown. The effect of extract towards MCF-7 breast cancer cell lines and Vero cells were observed using in vitro cytotoxicity assay to indicate its active fractions and its half maximal inhibitory concentration (IC50). Purified sample gave a rational effect towards MCF-7 breast cancer cells with IC50 value of 5.85 µg mL-.[23]

Ginseng *(Panax ginseng)*, which is traditionally used in some parts of the world as a popular remedy for various diseases including cancer. It was hypothesized that the ginsenoside Rp1, a component of ginseng, reduces cancer cell proliferation through inhibition of the insulin-like growth factor 1 receptor (IGF-1R)/Akt pathway. Firstly, the efficacy of Rp1 was tested against human breast cancer cell lines. Treatment with Rp1 inhibited breast cancer cell proliferation and inhibited both anchorage-dependent and -independent breast cancer cell colony formation. In addition, to it the treatment with 20 µM Rp1 induced cycle arrest and apoptosis-mediated cell growth suppression. Findings further indicated that Rp1 decreased the stability of the IGF-1R protein in breast cancer cells. Therefore, it is suggest that Rp1 has potential as an anticancer drug and that IGF-1R is an important target for treatment and prevention of breast cancer .[24]

Roots of *Pfaffia paniculata* have been well documented for multifarious therapeutic values and have also been used for cancer therapy in folk medicine. Study has been performed in a human breast tumor cell line, the MCF-7 cells. These are the most commonly used model of estrogen-positive breast cancer, and it has been originally established in 1973 at the Michigan Cancer Foundation from a pleural effusion taken from a woman with metastatic breast cancer. Butanolic extract of the roots of *P. paniculata* showed cytotoxic effect MCF-7 cell line, as determined with crystal violet assay, cellular death with acridine orange/ethidium bromide staining, and cell proliferation with immunocytochemistry of bromodeoxyuridine (BrdU). Subcellular alterations were evaluated by electron microscopy. Cells treated with butanolic extract showed degeneration of cytoplasmic components and profound morphological and nuclear alterations. The results show that this butanolic extract indeed presents cytotoxic substances, and its fractions merit further investigations.[25]

The plant *Podophyllum peltatum* produces podophllyotoxin, a resin, throughout the entire plant but especially in the rhizome. It is produced as a form of protection from insects and other herbivores. When ingested it causes gastroenteritis or even death in humans. Edema (swelling) and eventual deterioration of the spinal cord, brainstem, cerebellum, and cerebral cortex have been reported in rats treated with various amounts of the toxin. Toxicities of other organs (although not specifically mentioned) have been documented

Historically, this plant was widely used as a Chinese herbal medicine because it is a wild Asian plant. It was used to treat snakebites, general weakness,

poisons, condyloma accuminata, lymphadenopathy, and certain tumors. It was also used by the Penobscot Indians to treat cancer.[26]

Three anthraquinones, Cdc25B phosphatase inhibitors, were isolated from the methanolic extract of the roots of *Polygonum multiflorum Thunb. (Polygonaceae)*. Anthraquinones, physcion , emodin, and questin , inhibited the enzymatic activity of Cdc25B phosphatase with IC_{50} values of 62.5, 30, and 34μgmL^{-1}, respectively. Emodin and questin strongly inhibited the growth of human colon cancer cells, SW620 with GI_{50} values of 6.1 and 0.9μgmL^{-1}, respectively. Commercially available anthraquinones, chrysophanol, and rhein also inhibited Cdc25B phosphatase with IC_{50} values of 10.7 and 22.1μgmL^{-1}, respectively.[27]

Three toxic proteins and one agglutinin were purified from the seeds of *Ricinus communis* by simple and fast method using Sepharose 4-B affinity chromatography followed by Sephadex G-100 gel filtration. The weakly adsorbed ricins A and B were retarded and eluted with the buffer from the affinity chromatographic column, while *ricin C* and *ricinus agglutinin* had to be eluted with 0.1 M galactose. The molecular weights of ricins A, B, and C were about 62,000 and that of *ricinus agglutinin* was 120,000, estimated by amino acid compositions and SDS gel electrophoresis. They all possessed two non-identical subunits: A and B chains linked by one disulfide bond. Their LD50 values were 4, 28, 14 and 112 micrograms per kg body weight of mice for ricins A, B and C and ricinus agglutinin, respectively. The amino acid compositions of the three toxins and their A and B subunits were very similar, but not identical, while ricinus agglutinin showed a different composition. Ricin A is a newly isolated lectin which has a strong inhibitory effect on the growth of tumor cells. By using cell cultures, it was demonstrated that the tumor cells were more sensitive to lectin than non-transformed cells, and that this could be caused by the higher binding affinity of lectin to tumor cells than to non-transformed cells.[28]

Barley and wheat: Lunasin, a unique 43 amino acid, 4.8 kDa cancer-chemopreventive peptide initially reported in soybean and now found in barley and wheat, has been shown to be cancer-chemopreventive in mammalian cells and in a skin cancer mouse model against oncogenes and chemical carcinogens. To identify bioactive components in traditional herbal medicines and in search for new sources of lunasin, we report here the properties of lunasin from *Solanum nigrum L.* (SNL), a plant indigenous to northeast Asia. Lunasin was screened in the crude extracts of five varieties of the medicinal plants of *Solanaceae* origin and seven other major herbal plants. An *in vitro* digestion stability assay for measuring bioavailability was carried out on SNL crude protein and autoclaved SNL using pepsin and pancreatin. A nonradioactive histone acetyltransferase (HAT) assay and HAT activity colorimetric assay were used to measure the inhibition of core histone acetylation. The inhibitory effect of lunasin on the phosphorylation of retinoblastoma protein (Rb) was determined by immunoblotting against phospho-Rb. Lunasin isolated from autoclaved SNL inhibited core histone H3 and H4 acetylation, the activities of the HATs, and the phosphorylation of the Rb protein. Lunasin in the crude protein and in the autoclaved crude protein was very stable to pepsin and pancreatin in vitro digestion, while the synthetic pure lunasin was digested at 2 min after the reaction. It was conclude that lunasin is a bioactive and bioavailable component in SNL and that consumption of SNL may play an important role in cancer prevention.[29]

Solanum nigrum L. (SNL) has been traditionally used as a herbal plant, whose fruit is believed to have anti-tumor properties, although the mechanism for the activity remains to be elucidated. An ethanol extract from ripe fruits of SNL was prepared and investigated the mechanism involved in its growth-inhibitory effect on MCF-7 human breast cancer cells. Results from proliferation assay using tritium uptake showed that the proliferative capacity of MCF-7 cells was strongly suppressed in the presence of SNL ethanol extract. This was further confirmed through MTT assay and trypan blue exclusion experiments, which showed a very close correlation between the SNL extract concentration and the surviving cell numbers. The SNL extract-mediated suppression of cell growth was verified to be apoptotic, based on the appearance of DNA laddering, increase in DNA fragmentation, and low fluorescence intensity in nuclei after propidium iodide staining of the cells. Furthermore, the SNL extract was revealed to be a potential scavenger of hydroxyl radicals and DPPH radicals rather than superoxide anions. Collectively, findings suggest that SNL fruit extract could be used as an anti-oxidant and cancer chemo-preventive material.[30]

The DNA topoisomerase inhibitor β-lapachone is a quinone obtained from the bark of the lapacho tree (*Tabebuia avellanedae*) in South America. It has been reported to possess a wide range of pharmacological properties, and is a promising cancer chemopreventive agent. The effects of β-lapachone on the growth of the human hepatoma cell line HepG2 were investigated. The results showed that β-lapachone inhibits the viability of HepG2 by inducing apoptosis, as evidenced by the formation of apoptotic bodies and DNA fragmentation. Reverse

transcription-polymerase chain reaction and immunoblotting results indicated that treatments of cells with β-lapachone resulted in down-regulation of anti-apoptotic Bcl-2 and Bcl-X_L and up-regulation of pro-apoptotic Bax expression. β-Lapachone-induced apoptosis was associated with a proteolytic activation of caspase-3 and -9 and degradation of poly(ADP-ribose) polymerase protein. However, β-lapachone treatment did not affect the inhibitor of apoptosis proteins family and the Fas/FasL system. Taken together, our study indicated that β-lapachone may have potential as a chemopreventive agent for liver cancer.[31]

The taxane diterpenoid from *Taxol* was first reported in 1971, but it has only recently been recognized as a highly effective anticancer drug. The history of taxol's development is reviewed with an emphasis on the problems that almost prevented the discovery of its clinical activity, and on the key factors that kept it under investigation. Recent research on the structure-activity relationships and the synthesis of *taxol* is also reviewed.[32]

In the determination the antioxidant and anti cancer effects of *Essiac*, a tea prepared from a mixture of four herbs *Arctium lappa, Rumex acetosella, Ulmus rubra and Rheum officinale*, found that *Essiac* inhibited hydroxyl radical-induced lipid peroxidation by up to 50% at the 50% tea preparation concentration. These data indicate that *Essiac* tea possesses potent antioxidant and DNA-protective activity, properties that are common to natural anti-cancer agents. This study may help to explain the mechanisms behind the reported anti-cancer effects of *Essiac*.[33]

The activity of *Uncaria tomentosa* preparations on cancer cells was studied using in vitro and in vivo models. IC (50) values were calculated for preparations with different quantitative and qualitative oxindole alkaloid composition: B/W(37) --bark extracted in water at 37 °C, B/W(b)--bark extracted in boiling water, B/50E(37) --bark extracted in 50% ethanol at 37 °C, B/E(b)--bark extracted in boiling 96% ethanol, B/96E(37) --bark extracted in 96% ethanol at 37 °C and B/SRT--bark extracted in water and dichloromethane. Generally, the results obtained showed a high correlation between the total oxindole alkaloid content (from 0.43% to 50.40% d.m.) and the antiproliferative activity of the preparations (IC(50) from >1000 μg/ml to 23.57 μg/ml). B/96E(37) and B/SRT were the most cytotoxic preparations, whereas the lowest toxicity was observed for B/W(37). B/96E(37) were shown to be active against Lewis lung carcinoma (LL/2) [IC(50) =25.06 μg/ml], cervical carcinoma (KB) [IC(50) =35.69 μg/ml] and colon adenocarcinoma (SW707) [IC(50) =49.06 μg/ml]. B/SRT was especially effective in inhibiting proliferation of cervical carcinoma (KB) [IC(50) =23.57 μg/ml], breast carcinoma (MCF-7) [IC(50) =29.86 μg/ml] and lung carcinoma (A-549) [IC(50) =40.03 μg/ml]. Further animal studies on mice bearing Lewis lung carcinoma showed significant inhibition of tumor growth by B/W(37) administered for 21 days at daily doses of 5 and 0.5 mg (p=0.0009). There were no significant changes in the cell cycles of tumor cells with the exception of cell decrease at the G_2/M phase after the administration of B/96E(37) at a daily dose of 0.5 mg and the G(1)/G(0) cells cycle arrest demonstrated after the B/SRT therapy at a daily-dose of 0.05 mg. All tested preparations were non-toxic and well tolerated.[34]

Cycloviolacin O2 (CyO2), a cyclotide from *Viola odorata (Violaceae)* has antitumor effects and causes cell death by membrane permeabilization. In the breast cancer line, MCF-7 and its drug resistant subline MCF-7/ADR, the cytotoxic effects of CyO2 (0.2-10 microM) were monitored in the presence and absence of doxorubicin (0.1-5 microM) using cell proliferation assays to establish its chemosensitizing abilities. SYTOX Green assays were Sperformed to verify membrane permeabilization and showed cellular disruption correlates with cyclotide chemosensitization. Fluorescence microscopy studies demonstrated increased cellular internalization of doxorubicin in drug resistant cells when coexposed to CyO2. Interestingly, CyO2 did not produce significant membrane disruption in primary human brain endothelial cells, which suggested cyclotide specificity toward induced pore formation in highly proliferating tumor cells. Furthermore, three novel cyclotides (psyle A, C and E) from *Psychotria leptothyrsa (Rubiaceae)* were also monitored for cytotoxic activity. The cyclotides displayed potent cytotoxicity (IC50 = 0.64->10 microM), and coexposure to cyclotides significantly enhanced doxorubicin induced toxicity (IC50 = 0.39-0.76 microM). This study documents several cyclotides with robust cytotoxicity that may be promising chemosensitizing agents against drug resistant breast cancer.[35]

Viscum album agglutinin-1 (VAA-1) from where it is found is assumed to be the biologically most active ingredient of mistletoe extracts that are often used as adjuvant cancer therapy. To develop new approaches for lung cancer treatment, the antinewplastic activity of the evaluated the antineoplastic activity of VAA-1 was evaluated in combination with other chemotherapeutic drugs, including doxorubicin, cisplatin and taxol in the human lung carcinoma cell line A549.[36]

Detailed methods for in *vitro/in vivo* evaluation of anticancer drugs, with special reference to mistletoe

extracts from plant *Viscum Album*, have been reviewed. Mistletoe extracts have been shown to possess significant antitumor activity, *in vivo*, against murine tumors, Lewis lung carcinoma, colon adenocarcinoma 38 and C3H mammary adenocarcinoma 16/C. Methods for the extraction of biologically active alkaloids from mistletoe and their anticancer activities are presented. The possible origin of alkaloids in mistletoe plants, and their contributions towards a mechanism of anticancer activities of mistletoe extracts, were proposed.[37]

Proanthocyanidins (PAs), also known as condensed tannins, are naturally occurring oligomers and polymers of flavan-3-ol monomer units widely found in the leaves, flowers, fruits, seeds, nuts and barks of many plants. Grape seed *(Vitis vinifera L.)* proanthocyanidins (GSPs) which have been used as nutritional supplements and , as antioxidants, which prevents in preventing atherosclerosis and cardiovascular diseases. The anthracycline antibiotic adriamycin (Doxorubicin, DXR) is a cancer chemotherapeutic agent that interferes with the topoisomerase II enzyme and generates free radicals. In the present study, GSPs (1.680, 3.375, or 6.750 mg/mL) alone were examined for genotoxicity, and combined with DXR (0.125 mg/mL) for antigenotoxicity, using the standard (ST) and high bioactivation (HB) versions of the wing somatic mutation and recombination test in Drosophila melanogaster. The results observed in both crosses were rather similar. GSPs themselves did not show genotoxicity at the doses used but they suppres the DNA damage induced by DXR in a dose-dependent manner. Comparison of the frequencies of wing spots in the marker-heterozygous (MH) flies and balancer-heterozygous (BH) flies from both crosses, indicated that induced recombination was the major response for the treatments with DXR alone. The co-treatments demonstrated that GSPs have some anti-mutagenic activity; however, anti-recombinagenic activity was the major-response.[38]

Vitis Vinifera :- Investigations were carried out for evalution of antitumor and antioxidant activity of Ethanolic extract of *vitis vinifera* L.Leaves. For its antitumor, antioxidant activity in Ehrlich ascites carcinoma (EAC) induced swiss albino mice. The antitumor effect and antioxidant role was assessed using tumor volume, packed cell volume and estimation of liver LPO and antioxidant enzymes such as SOD, CAT. The Ethanolic extract administered at 200 and 400 mg/kg b.w.per day for 14 days, after 24 hours of tumor inoculation. Treatment with extract at a dose of 200 and 400 mg/kg increased mean survival time. Treatment with extract also decreased the levels of LPO and increased the levels of superoxide dismutase, catalase. The results suggest that ethanolic extract of *vitis vinifera* possess significant antitumor, antioxidant effects in EAC tumor bearing mice.[39]

Zingiber officinale:- Ginger may act as an anti-cancer and anti-inflammatory agent by inactivating NFkappaB through the suppression of the pro-inflammatory TNF-alpha.[40]

Some Anticancer Natural Products: [41]

Name	Biological source	Geographical source	Chemical constituent	Uses
Aconite	Dried root of *aconitum napellus, Ranunculacece*	Hungary, germany, spain Switzerland	Aconitine, hypaconitine, neopelline, napelline, neoline	Treatment of rheumatism, inflammation.
Allium Sativum (Garlic)	Bulb of the plant know as *allium sativum, lilaceae*	Central asia, southern Europe, USA and India	Carbohydrate, protein (albumin), fat, mucilage	Carminative, aphrodisiac, expectorant, stimulant, disinfectant
Artemisia	Unexpanded flower heads of *Artemisia cina, Artemisia buvifolia wall, Artemisia maritime, compositae*	Pakistan, turkey, from Kashmir to kumaon in Himalayas	Essential oil, santonin, artemisin	Anthelmintic

Name	Biological source	Geographical source	Chemical constituent	Uses
Camellia sinensis	Prepared leaves and leaf buds of *Thea sinensis, Theaceae*	India, Shri lanka., china, Indonesia, japan	Caffeine, theobromine, theophylline, gallatonic acid	CNS stimulant, diuretic
Comptotheca accuminata	Dried stem wood of *comptotheca acuminate, nyssaceae*	China, Tibet, southern china	Quinoline alkaloid, camtothecin, 10 hydroxy camptothecin, 10 methoxy camptothecin	DNA topoisomerase Iinhibitors, antitumour, antileukemia
Catharanthus roseus	Dried whole plant of *catharanthus roseus, apocunaceae*	South africa, india, USA, Europe, australia	Vincristine, vinblastine, ajmalicine	Antineoplastic, acute leukemia, hodgkin's disease
Curcuma longa	Dried as well as fresh rhizome of the plant known as *curcuma longa, zingiberaceae*	Tamil Nadu, Andhra Pradesh, kerala	Curcuminoids, curcumin, volatile oil, starch	Anti inflammatory, anti arthritic, cervical cancer
Glycyrrhiza glabra	Dried peeled or unpeeled root and stolon of *glycyrrhiza glabra, leguminosae*	Spain, sicily, England	Glycurrhizin, glycyrrhizinic acid which on hydrolysis yield glycyrrhetinic acid	Expectorant, demulcent, antigastric effect
Panax ginseng	Dried root of *panax ginseng, Araliaceae*	Korea, china, Russia, Canada, USA	Ginsenoisides, panaxosides, chikusetsusaponin	Immunomodulatory drugs
Podophyllum peltatum	Dries rhizomes and root of *podophyllum peltatum, barberidaceae*	From Kashmir to Sikkim and parts of U.P	Podophyllin, podophyllotoxin, alpha and beta peltatins	Cytotoxic action, treatment of veneral, purgative
Taxus brevifolia	Dried leaves, bark and root of various species of *taxus, taxaceae*	India, Canada, America	Taxane, cephalomannine, 10-deacetyl baccatin, taxol	Lung carcinoma, gastric and cervical cancers and also carcinomas of head, neck, prostate and colon
Viola odorata	Dried aerial parts obtained from *viola odorata, violaceae*	India (Kashmir, himachal Pradesh, kumaon hills)	Essential oil, alkaloid, saponins, glycoside of methyl salicylate.	Expectorant, diaphoretic, antipyretic, antibacterial
Zingiber	Rhizomes of *zingiber officinale roscoe, zingiberaceae*	South asia, Africa, Australia, Mauritius, jamaica, Taiwan, india.	Volatile oil, starch, fat, fibre, inorganic material, residual moisture, acrid resinous matter.	Stomachic, aromatic, carminative, stimulant, flavouring agent.

Conclusion:

Medicinal plants have contributed a rich health to human beings. Plant extracts and their bioactive compounds present in them which are responsible for anticancer activity have to be screened for their valuable information. This review had given some of the plants possessing anticancer activity for various types of cancer. This review can help others to explore herbs to further extent and its use in various other disease and toxicity studies along with clinical trials.

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